ALINEA

NUTRITION

MAY 2022

www.alineanutrition.com

TABLE OF

CONTENTS

What We Know, Think We Know, or Are Starting to Know 03

The Study 04

Results 05

The Critical Breakdown 06

Key Characteristic 06

Interesting Finding 07

Relevance 07

Application to Practice 08

References 09-10

Kühn L, MacIntyre UE, Kotzé C, Becker PJ, Wenhold FAM. Twelve Weeks of Additional Fish Intake Improves the Cognition of Cognitively Intact, Resource-Limited Elderly People: A Randomized Control Trial. J Nutr Health Aging. 2022;26(2):119-126.

What We Know, Think We Know, or Are Starting to Know

We know that there are major concerns over the predicted increase in prevalence of neurodegenerative diseases like dementia and Alzheimer' s Disease [AD], due to the absence of any real effective pharmacological interventions to arrest or reverse these conditions [(1)].

This astonishing failure rate of drug development for dementia/AD has squarely placed the emphasis on early intervention. Cognitive decline is a spectrum, and from a dietary perspective it appears that the earlier the intervention, ideally before or at the stage of mild cognitive impairment [MCI], the better [(2–4)].

Of the potential foods and nutrients of interest for the brain, fatty fish and its primary components, eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA], have been centre-stage since the early epidemiology of diet and dementia risk showed significantly lower risk from intakes of these foods and nutrients [(5–8)].

However, there is a disconnect between the findings from cohort studies and interventions testing supplemental EPA/DHA, which may reflect differences between food vs. nutrient exposures, lack of sufficient duration of intervention studies, and the baseline cognitive health and stage of cognitive decline of the participants [(9–11)].

One noticeable feature of the intervention studies to date is the use of omega-3 supplements, rather than foods. The present study was a food-based intervention on the effects of oily fish on cognitive function in older adults.

The Study

The study was conducted in Gauteng, South Africa, in participants over 59yrs of age and without cognitive impairment, living independently in a retirement centre. The study was conducted in two separate phases: a non-intervention 12-week period followed by a 12-week intervention period.

For the first, non-intervention period, participants underwent cognitive testing at baseline and then continued for 12-weeks in their normal routine and diet. Participants then underwent testing again at the end of that 12-week period, following which they began their assigned diet for a further 12-weeks before final testing post-intervention.

The study used a version of the MIND diet modified for foods available in South Africa, in all participants, with the intervention group adding oily fish. Participants were thus randomised to one of two diets:

- **Intervention:** Modified MIND diet + weekly oily fish [sardines and anchovy fish paste]
- **Control**: Modified MIND diet + meatballs and texturised soy protein

Participants in the intervention group were provided with two 410g cans of sardines and 75g anchovy fish paste per week; those in the control group were given two 410g cans of meatballs and 200g texturised soy protein per week. The primary outcome was change in the Cognitive Abilities Screening Instrument [CASI] between the start of the intervention period and end of the 12-week intervention. The CASI scores from 0-100 and is a validated instrument in community samples [12].

Results: 51 participants completed the intervention period [31 and 26 in the intervention and control groups, respectively]. 74% of participants were female and the average age was 72.7yrs.

- ***Omega-3 Intake/Levels*:** Total omega-3 fatty acids after 12-weeks were 1,359mg/d and 724mg/d in the intervention and control groups, respectively. RBC EPA+DHA levels were 5.91% and 5.60% in the intervention and control groups, respectively.
- ***MIND Diet Adequacy Scores [0-15]*:** Total MIND diet adequacy after 12-weeks was 8.44/15 and 8.93/15 in the intervention and control groups, respectively.
- ***CASI Scores*:** After 12-weeks, participants in the intervention group scored 2.3 points higher [mean score 93.3, 95% CI 91.8 to 95.1] compared to the control group [mean score 91.1, 95% CI 89.2 to 93.0]. Of the subdomains score out of 10, significant differences were observed for visual construction [8.81 vs. 7.54 in the intervention and control groups, respectively].

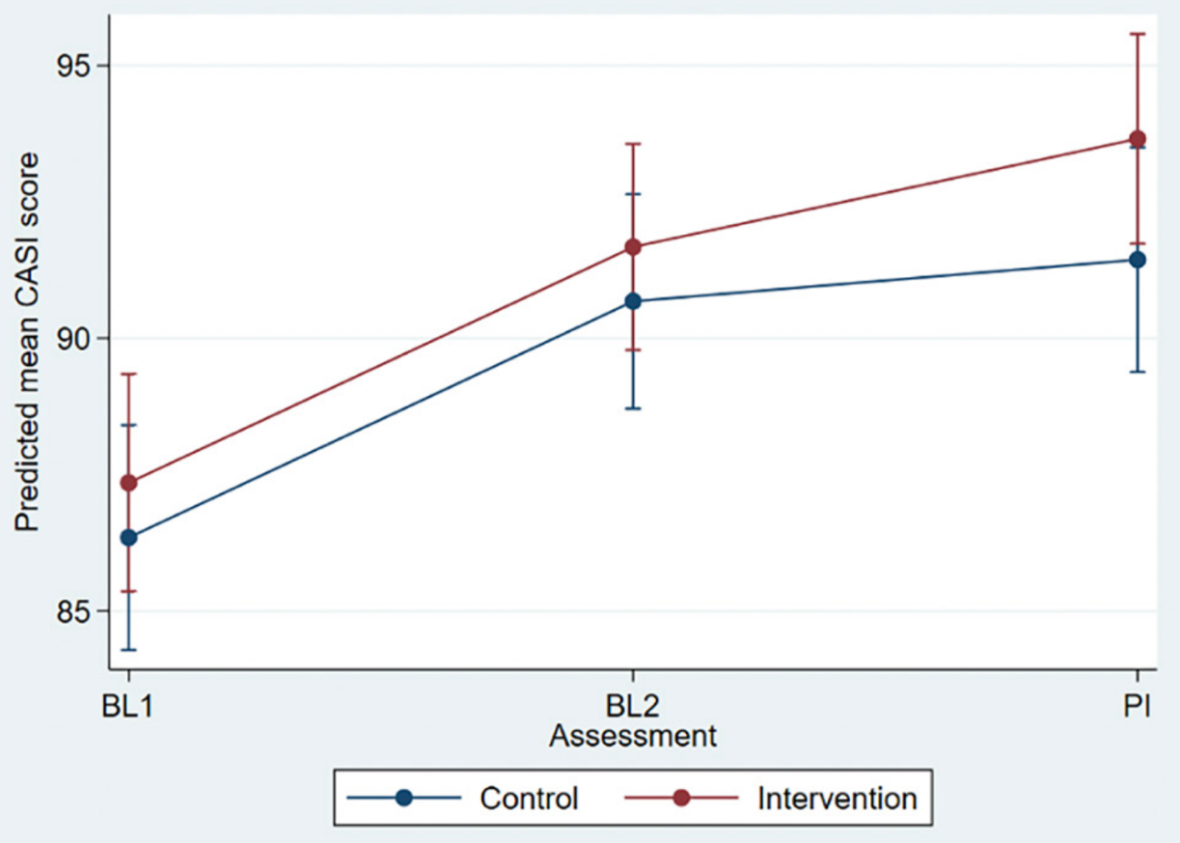

Figure *from the paper illustrating the change in CASI scores [out of a total score of 100] between each phase of the study. BL1 represents the start of the 12-week non-intervention phase, while BL2 is the start of the 12-week intervention period. PI is 'post-intervention', after the 12-week intervention period. As you can see, the CASI scores increased in both groups between BL1 and BL2, which indicates the potential for a habituating effect of taking the test [i.e., participants get better at taking the test due to familiarity]. However, there was no difference between groups in this phase, and scores appeared largely similar in the control group between BL2 and PI.*

The Critical Breakdown

Pros: Randomisation was conducted by an independent moderator blinded to the intervention. It is a strength that both groups had the same basic MIND-diet modifications, thus aiming to have fatty acid composition of diet as the major distinction between groups. The study was clearly designed with sensitivity, for example, all who gave consent to participate in the study were provided with study foods irrespective of whether they subsequently met the inclusion criteria or not. This meant that the provision of foods did not oblige people anyone to participate. The population studied were resource-limited, living on total monthly incomes of less than $223 USD per month, which is quite novel to see relative to the typical demographic in more affluent Western study populations. It indicates that food-based interventions could be applied in resource-limited populations, albeit the caveat with that point is that study foods were provided. Red blood cell [RBC] measures omega-3 fatty acids were used to assess adherence, in addition to self-reported adherence.

Cons: The intervention is very poorly defined. For example, the paper states that the participants were given 810g of sardines and 75g anchovy paste per week; but there does not seem to be more specific details on targeted daily intakes. The paper states that *"both groups perceived the study foods to be excessive and chose not to take all of the foods weekly."* Ok, so who took what? How much did the intervention group consumed? The paper states that participants were asked to record intake and hand back empty containers to assess compliance, but these data don' t appear in the paper. The lack of clear prescription and defined intervention is a limitation of the present study. The study estimated a required sample size of 44 participants per group, thus with 31 and 26 in the intervention and control groups, respectively, the study was likely underpowered to detect differences between groups. The baseline non-intervention period may have resulted in a habituating effect on completing the CASI, evident in the increase in scores over the 12-week non-intervention period.

Key Characteristic

Without doubt the fact that this was a food-based intervention targeting oily fish intake makes it relatively unique in the research on omega-3 fatty acids and cognition. In a study in adolescent schoolchildren in Norway, the effects of consuming oily fish was compared to the effects of omega-3 supplementation over 12-weeks [(13)]. At baseline, intakes of salmon, mackerel and herring were associated with better cognitive processing speed; however, there were no significant associations between nutrient status and cognitive outcomes after the intervention period.

Nevertheless, this Norwegian trial is instructive of the methodological issues facing this area of research: participants were regular oily fish consumers in the home, reflecting the habitual population diet, nearly half of participants consumed omega-3 supplements, and baseline Omega-3 Index [O3I] levels [RBC EPA+DHA] were 5.8%, in a range that we might expect to see little additional benefit to additive omega-3 intake [(14)].

The present study is not without these issues; some participants were using omega-3 supplements [although most were not], and RBC EPA+DHA levels were 5.60% in the control group, which may mean a lack of effective contrast to determine stronger effects. And the lack of substantial difference in the measured levels of RBC EPA + DHA compared to the substantial difference in estimates of dietary intake of omega-3 fatty acids from the dietary assessment may suggest some lack of compliance and/or measurement errors. Nevertheless, conducting this study as a food-based intervention is an important characteristic in an area of research dominated by supplement studies.

Interesting Finding

Of the cognitive domains that make up the total CASI score, the only subdomain which showed a significant difference between groups was for visual construction. Now, why is this interesting? Because improvements in various parameters of visual acuity are one of the more well-established effects of omega-3 fatty acids, particularly DHA. In early infancy and children, visual development is dependent on adequate DHA [in addition to AA] [15,16].

In adults, there is also some evidence of improved visual capacities. For example, in an intervention study which tested the effects of 900mg/d DHA supplementation, visual-spatial cognitive testing improved over 24-weeks in older adults with age-related cognitive decline [10]. Thus, it is interesting that the difference between groups in the present study was primarily driven by changes in a visual construction, which is a domain of cognition that becomes dysfunctional in dementia/AD [17]. It appears that long-chain omega-3 fatty acids are important for visual neurodevelopment over the lifespan.

Relevance

This study primarily catches the eye because of the food-based focus of the intervention and control group, and because of the low-income and more resource-limited population group. It is also good to see a control group that consumed a broadly similar background modified MIND diet, which was a positive design feature to try and isolate effects of the differences in omega-3 fatty acid intakes from the oily fish.

The study also highlights the ongoing need for important variables to be considered in designing any intervention trial on the effects of EPA/DHA on cognitive health: larger sample sizes, meaningful comparisons in omega-3 status, and more thorough screening for regular fish and/or supplement use.

For example, a study in Germany comparing >6.8% O3I to <5.7% showed a significantly higher odds of cognitive impairment and dementia in the lowest group, compared to the highest [14]. In the present study, the levels of RBC EPA+DHA were similar between groups, and sitting around the lower level as the aforementioned German study. If higher levels had been achieved in the intervention group in the present study, would this have strengthened the findings?

In considering that question, we should note that the participants in the present study were not cognitively impaired and scored highly on the CASI before the intervention. This may mean that there was little overall room for improvement. The effect size is small, although the difference in visual construction is consistent with wider knowledge and may plausibly reflect a genuine effect of the intervention.

Application to Practice

The question over the 'need' for long-chain omega-3 fatty acids for cognitive health is certainly not resolved by the present study. And the wider evidence remains, in general, contentious. Whether there is any difference between omega-3 intakes from foods vs. supplements will need to be teased out in future research. Nevertheless, the present study suggests some additional benefit to oily fish in the context of a modified MIND diet, compared to a MIND diet without additional oily fish intakes.

This would, of course, be consistent with the actual mind diet itself, which makes specific recommendations for oily fish intake [minimum dose of 1/week], and for which high adherence to the MIND diet appears more beneficial than either a Mediterranean or DASH dietary pattern [18,19]. All lines of evidence considered, I remain of the opinion that a direct source of EPA+DHA is preferable to none for long-term cognitive health across the lifespan.

References

1. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimers Res Ther. 2014;6(4):37.
2. Dominguez LJ, Barbagallo M. Nutritional prevention of cognitive decline and dementia. Acta Biomedica. 2018;89(2):276–90.
3. Morris MC. Nutritional determinants of cognitive aging and dementia. Proceedings of the Nutrition Society. 2012;71(1):1–13.
4. Jennings A, Cunnane SC, Minihane AM. Can nutrition support healthy cognitive ageing and reduce dementia risk? BMJ. 2020;369:m2269.
5. Kalmijn S, van Boxtel MPJ, Ocké M, Verschuren WMM, Kromhout D, Launer LJ. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurology. 2004;62(2):275–80.
6. Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS. Fish consumption and cognitive decline with age in a large community study. Archives of Neurology. 2005;62(12):1849–53.
7. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Archives of Neurology. 2003;60(7):940–6.
8. Barberger-Gateau P, Letenneur L, Deschamps V, Pérès K, Dartigues JF, Renaud S. Fish, meat, and risk of dementia: Cohort study. British Medical Journal. 2002;325(7370):932–3.
9. Cunnane SC, Chouinard-Watkins R, Castellano CA, Barberger-Gateau P. Docosahexaenoic acid homeostasis, brain aging and Alzheimer's disease: Can we reconcile the evidence? Prostaglandins Leukotrienes and Essential Fatty Acids. 2013;88(1):61–70.
10. Yurko-Mauro K, McCarthy D, Rom D, Nelson EB, Ryan AS, Blackwell A, et al. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimer's and Dementia. 2010;6(6):456–64.
11. Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, van Dyck C, et al. Docosahexaenoic Acid Supplementation and Cognitive Decline in Alzheimer Disease. JAMA. 2010;304(17):1903.
12. Cullen B, O' Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. Journal of Neurology, Neurosurgery & Psychiatry. 2007;78(8):790–9.
13. Handeland K, Skotheim S, Baste V, Graff IE, Frøyland L, Lie Ø, et al. The effects of fatty fish intake on adolescents' nutritional status and associations with attention performance: results from the FINS-TEENS randomized controlled trial. Nutrition Journal. 2018;17(1):30.
14. Lukaschek K, von Schacky C, Kruse J, Ladwig KH. Cognitive Impairment Is Associated with a Low Omega-3 Index in the Elderly: Results from the KORA-Age Study. Dementia and Geriatric Cognitive Disorders. 2016;42(3–4):236–45.
15. Cheatham CL, Colombo J, Carlson SE. n−3 Fatty acids and cognitive and visual acuity development: methodologic and conceptual considerations. The American Journal of Clinical Nutrition. 2006;83(6):1458S-1466S.
16. SanGiovanni JP, Parra-Cabrera S, Colditz GA, Berkey CS, Dwyer JT. Meta-analysis of Dietary Essential Fatty Acids and Long-Chain Polyunsaturated Fatty Acids as They Relate to Visual Resolution Acuity in Healthy Preterm Infants. Pediatrics. 2000;105(6):1292–8.

References

17. Possin KL. Visual spatial cognition in neurodegenerative disease. Neurocase. 2010;16(6):466–87.

18. Bennett DA, Aggarwal NT. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND diet associated with reduced incidence of Alzheimer' s disease. 2016;11(9):1007–14.

19. Morris MC, Tangney CC, Wang Y, Barnes LL, Bennett D, Aggarwal N. MIND diet score more predictive than DASH or Mediterranean diet scores.. Alzheimer' s & Dementia. 2014;10(4S):166.